### PATENT COOPERSANOS FREATY

From the INTERNASIONAL PROTE	MINARY EXAMINENCIAL ELEGICAN	u / JUL ŽUĆ	i ki	
To: Anand and Anand Advocates Bs4' Noanandóin East 1!0013 New Delhi		2	PCT  NOTE: A DOM OF TRANSMITTAL OF A LESS ALOOM OF PRELIMINARY EXAMINATION REPORT	
Estin			(PCL Rate 71.1)	
			2 9 JUN 2004	
Applicant's or agent's file 1:352(PCT59)	reference	. 17:	PORTANT NOTIFICATION	
hucummaaa Application PCTAN2003/000383	So International Files 5 December 200		Promis Date 5 December 2003	
A copy of the the elected O  Where round	ffice.	s inneres it any estable g transfranted to the fair garman and dopelo, wi	olard on the international application material Bureau for construction to all it prepare an English translation of the report	
REMINDER	t .			
and paying it.		e growery date out lader	perfecting certain acts (filing translations in some Offices)(Article 39(1))(see also the	
Where a grans	Sanon of the interpretarial reminances	masi hi shriished a a	n elected Office, that manslation must contain	
prepare and fo	Many annexes to the international pro- urnish such translation directly to each	liminary crantination r	eport. It is the applicant's responsibility to	

Name and mailing address of the IPEA/At

AUSTRALIAN PATENT OFFICE PO BOX 200 WOOPN ACT 2606 AUSTRALIA is not taldress perferipensatidation in the simile No. 1021 6288-9529

-m/

TAN DOWD

Authorized officer

r (exercise to (83) 6283 2273

From Politikasi in dan 1997a

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

ARIA ALLE THAT THE TANK

Applicants of agends tile reference 11.452(PCT59)	FOR FURTHER ACTION	Son Surrounded of Continuital of Laternational Findinguage  Environment Report Design PULL Device 4404		
	Interpote cally reports  into respect to the control of the contro	The same the same and according		
PCT/IN2003/000383	Sileopolise 2000	Table table that		
International Patent Cheerfe Stop (1967), or	วิธีกำลงใบโรคสุโมฮ์ชา และ	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1		
Int. Cl. 1 + 0.7D 498/48				
Applicant		The same of the sa		
BIOCON INDIA LIMITED et a				
<ol> <li>На инститений распинату ехазаны в bansunted to the apple and оссотыя.</li> </ol>	tion report has been josepa e pri Arhela (br	and by this linear upone Circlinations Examinates Authority and		
A. This BI PORT consists of a high of (2)	- Kitarente - 1860 - eustgebeg styret (u)	Mrt steret		
Ass. species	**	cof the slowing their planes and or drawing, which have been		
amended and are the basis for this report and contacting receive thous made before this Anthony (see Rule 10.16) and Niction 607 of the Administrative Instruments under the PCT)				
These immercia common of a total c	d danggar			
3. This report combins indications relating	to the following dens.	- material contract contract of the contract o		
I X Basis of the report	•			
II Primity				
III   Non-establishment of op-	unds with regard to make:	o ravedy inventive step and indiannal applicability		
14 Lack of usary of myencic		W William C dock make naturation epopularity (1988)		
Reasoned statement under Article 35:21 with regard to novely, inventive step or industrial applicability:     citations and explanations supporting such statement.				
VI Curtain documents cited	and the second s			
VII Certain detects in the inte	nonacilique l'anultane			
VIII Certain observations, on the	he international applicatio	G.		
Date of submission of the demand	1 1)-	ne of completion of the report		
22 March 2004	<u> </u>	Jane 2004		
Name and maring address of the IPEA As		Remord विशिव्हर		
AUSTRALIAN PATENT OFFICE	:	<del>70</del> /		
POBOX 200, WODEN ACT 2604, ALSTRAS, Communications of profipostralia govern		x powp		
Facsimile No. 3924 8285 3929	3	N DOWD  leptone No. (62) 6287-7273		
And the state of t		Experience of the second commence of the seco		

# INTERNATION MEPRET MEN VEY ENAMINALED MARGE

International application 50

PCT/182003 000383

L. Basis of the rep	The same of the sa
1. With regard to the ele	CHERES OF THE CORE CORES OF A STORES OF THE CORES OF THE
He many	al application so programmy filed
X the Arsenptan	pages 2-7, as ongress steg
	pages . Skd with the deputed
	10000 1. Three-co on 18 June 2004 of the leads at 16 June 2004
j N On claims	pages 9-10, as eagenable rieg
	purva 🕠 as amended conferme with 20 or or over thooley Acted, [49]
	pages 8, the explant 18 Jame 2004 was first separat by June 2004
the attackings,	Page - Carongacin skyl
	pages . The description
1 11 111 5 78	paper . In circles, and the effect of
The sequence by	ting part of the description
	proper a so compressive fuer.
	Paper Contract with the demand
	Island . Interest on with the letter of
these elements were a	guage, all the elements marked above were as adapte on humalised to this Authority in the language in application was filled unless situs, whe indicated index this dominal formation of the Authority in the tellowing language—which is: It translation furnished for the purposes of international search (under Rule 23.1(b)).  publication of the any remonal application (note: Rule 48. (89))
er how wee	the translation furnished for the isoposis of international prefinitionly examination (under Rules 35.2
***************************************	deotide and/or amino acid sequence discussed in the international application, the international into was carried car on the basis of the sequence lixing
£	increational application in written form
2 ····	th the international application as computer resideble form
្រាំ ក៏នេះនៅនៅនេះ និងមិនទទ្ធា	nently in this Authority is written felin.
furnished subsequ	uently to this Authority in computer realithic form
The statement tha	n the ≥ubxoquently farmshed written sequence haring does not go beyond the disclusure in the Boution as filed has been farmshed
The statement tha begu furmshed	it the information securded in compares realiable form is identical to the written sequence listing has
L Libe amondments	have resplied in the cancellation of
ine descr	
the clans	
	ings, sheets fig
(	•
	run established as 11 (15 mc 90) die amendments had not been made, since thry have been considered to closure as their as indicated in the Supplemental Box (Rule 70.2(c)) ***
,.	ch have been formoned to the seconoug Colleg in response to an invitation under Article 14 are referred to in this als and are not unnexed to this repose stock bloods on the contain assemble und Albert 10 (b) and 20 (2)
* Engrephycomenishessy	entaining such amonday we must be represent to studies them. I can annexed to this require

#### PCT/AN2003/000383

V. Reasoned statement under Article 35(2) with regard to novelry, inventive step or industrial applicability; citations and explanations supporting such statement.

1	Statemen		
	Novelytha	Clarity 4-40	VUS
		Camp	<b>NO</b>
	Inventive step (18)	( xpms - 1-10	VES
		4 office	<b>V()</b>
	(Al) while of type landschaft	Common 1-10	VFS
		Clares	(N4.)

2 Citations and explanations (Rule 70.7)

This report is based on the decaments cired in the International Search Report.

- D1 US \$ 508 308 AT
- 112 USS 616 595 AT
- DN 1/5 4 734 492 AT
- 194 J. Antidnot (Tokyo) 1999 Max; 52(5), 300, 73
- DS UN 6 \$76 135 B)
- 106 US 6 492 513 BT

Novelty and Inventive Step-

None of the documents cited impings on the application for the purposes of novelty or inventive step

Industrial Applicability

All claims satisfy the requirements of maustical applicability

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

AND A BOOK A GROWN THE

Applicant's or age 11352(PC159)	nes fils systemate	FOR FURTHER ACTION	nge Suttigation of Transmitted of Informational Preliminary Execution Report (Form PCT/PEAST 6)	
International Application No		Interpetational burns Date	throng Darc olas month, seam	
PCT/IN2003/00	10383	5 December 1003	FOOD coloresest 2.1	
Internatural Pate	nt Classification (IP) for	national classics above so	; In	
Int CL (30)	) 498-18			
Applicant				
BIOCON	INDIA LIMITED et a			
<ol> <li>This international preliminary examination report to been proper to a true Internation # Preliminary Examining Anthonty and is transmitted to the applicant according to Article 55.</li> </ol>				
2 This RIPPH	Compass of a total of 13	short in wheel the co	sur dect	
This report is also accompanied by ANNEXhame, specifical the description, claims und/or drawings which have been amended and are the basis for this report and or directs realizations made before this Anthority (see Rule 70.16 and Section 60% of the Administrative Installed on stides the PCT).				
These is	mnever coprint of a local	3 sherin		
3. This report co	ntams indications relating	e to the following Rems	The second secon	
	Basis of the report			
	Pricess		or a second	
	,			
	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability		ty, in entire step and industrial applicationity	
	IV Lack of unity of invention		and the second s	
	V Reasoned statement under Artiste 35(2) with regard to povelty, inventive step or industrial applicability, ententions and explanations supporting such statement.			
VI	Certain documents eited			
N. S.	Certain defects in the im	ernazional applicacion		
VIII []	Certain observations on	the unerosusmai applicatio	771	
Date of submussion	n of the <b>dem</b> and		are of completion of the report	
22 March 2004			4 June 2004	
Name and making a	ddires of the IFEATAL	, 3	ufranted Officer	
AUSTRALIAN PAT			777 /	
PO BOX 200, WODEN ACT 2606, ALESTICAL Esmail address: perglipaustralia gos au		110	AN DOWD	
Fuestinite No. (02) 6285-3929		1	elephone No. (02) 6283-2273	
			A	

### IN HURNA FIONAL PRIEDMINARY ENAMINATION REPORT

International application No.

PCT/dN2003/000383

1	. Basis of the repo	#1			
	1. With regard to the chancuts of the international appropriate "				
	the international	Application as originally filed			
	X. The description.	pages 2-7. as originally nixd.			
		pages , filed with the constad.			
		pages 1, received on 18 June 2004 and the length of the land 2001			
	X  the classes.	pages 9-10, as minualis filed.			
		pages of as an ended they other with any of stimums order. Attended by			
;		paper Tiled was the convent			
	ı	pages 8. osterved on 38 June 2004, was the level of 16 June 2004			
	[ ] the drawings,	pages . wonganathy filed,			
		pages . tiled with the demand.			
	3	pages is recovered as a with the timen of			
	the sequence his	ing past of the description			
		pugrs . acongradiy tool			
		pages . tiled with the decland			
		pages , researched with the control			
(A.)	which the international These elements were a	guage, all the elements marked above were available or furnished to this Authority in the language in application was filed, indess otherwise gate doctor that make item, will able to furnish to this Authority in the tellowing language—which is a translation furnished for the purposes of mentional wards funder Rule 23 I(b)).			
	the Language of publication of the oversational applications and Ride 48,3(54)				
	the language of the and/or 55-3)	the translation formished for the purposes of international prviousinary examination funder Rules \$5.2			
	With regard to any nov	destide and/or amino acid sequence disclosed in the international application, the international			
	preliminary examina	nton was carried but on the basis of the sequence listing			
	contained in the	international application in wanter three			
	[ ] tiled together wi	th the international application in computer readable form.			
	furnished subsec	purally to this Authority to written form			
	turnished subsec	aently to tha Authority is computer coatable form			
	international appli	rodromation of Some had sometic equation which is the some operation and the constitution of the constitut			
	The statement the been furnished	tine information recorded in computer readable form is identical to the written sequence listing has			
4.	The amendments	have resulted in the cancellation of			
	the descr	lption, pages			
	the claum	s. Nos.			
	the draw	ngs. sheets/lip			
5. 	This report has be go beyond the disc	un established as if (some of) the animalments had not been made, smort they have been considered to closure as filled, as indicated in the Supplemental BootRule 70 Acry **			
*	Replacement sheets white report its "originally file	th him have formalied to the receives (1960) in response to no modulum under Article 14 are referred to in this d" and are on non-sed to this report some the old one contain amendments allales 70.26 and 70.17;			
<b>*</b> *		dulaning such immediations wises to referred or understant total innered to the expert			

#### PCT/IN2003/000383

V. Reasoned statement under Arbele 38(2) with regard to novelts, inventive step or industrial applicability; cuations and explanations supporting such statement

1 Statyment				
Novelty (N)	Charts 1-10		YES	
	Chamb		NO	
Insentive step (18)	Claims 1-10		VES	
	Claure		NO	
halustrad applicatishts (18)	Clarry 1-10		YES	
	Classes		NO	

3 Cultinus and explanations (Rule 10.7)

This report is based in the documents cated in the faternational Search Report

- D1 135 5 508 398 AT
- 102 Los 9 n lo 595 A 1
- D3 US 4 734 497 AT
- D4 J. Antibiot (Tokyo) 1999 May: 52(5), 466-73
- 105 US 6 576 135 B1
- Do US 6/497/513/R1

Novelty and Inventive Step

Some of the documents ened appinge on the application for the jumposes of nevelty or inventive step-

Industrial Applicability

All claims satisfy the requirements of industrial applicability

#### TITLE OF THE INVENTION

PROCESS FOR THE PURIFICATION OF MACROLIDES

### FIELD OF THE INVENTION

This invention relates to a process for purification of macrolides.

#### 10 BACKGROUND OF THE INVENTION

A compound, 15,19-Epoxy-3H-pyrido[2,1c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25, 26,26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3methoxycyclohexyl]-1-methyl ethenyl]-14,16-dimethoxy-15 4,10,12,18-tetramethyl-8-(2-propenyl)-, (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS), also known as FK506 as well as tacrolimus disclosed by EP 184162 and US 4,894,366 is useful as an immunosuppressant. Another compound, 15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21 20 (4H,23H)-tetrone,8-ethyl-5,6,8,11,12,13,14,15,16,17,18,19,24,25,26, 26a-hexadecahydro-5,19-dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3methoxycyclohexyl]-1-methylethenyl]-14,16-dimethoxy-4,10,12,18tetramethyl-, (3S,4R,5S,8R,9E,12S,14S, 15R,16S,18R,19R,26aS)-, 25 also known as immunomycin as well as FK 520, disclosed in EPO Publication No. 0184162 is also useful as an immunosuppressant. Many other derivatives of these compounds as well as structural

30

analogues have immunosuppressant property.

## 5 We claim:

20

25

- A process for the recovery of a macrolide in substantially pure form comprising:
  - treatment of an impure or crude macrolide with water immiscible solvent,
- b) optional concentration of the mixture,
  - treatment with ammonia gas to phase out impurities,
  - d) separation of impurities,
  - e) optional concentration of the phase containing the macrolide,
- f) loading on silica gel chromatography, optionally reversed phase or pretreated with silver, and elution of the macrolide,
  - g) affording the macrolide in substantially pure form,
  - optional repetition of step f and g to afford the macrolide in substantially pure form.
  - A process as in claim 1, wherein the macrolide is selected from tacrolimus, immunomycin or sirolimus.
  - A process as in claim 1, wherein the water immiscible solvent is selected from a group comprising hydrocarbons, heterocyclic compounds, ethers or esters.
  - 4. A process as in claim 1, wherein the water immiscible solvents is selected from a group comprising benzene, toluene, hexane, ethyl acetate, isobutyl acetate or butyl acetate.
  - 30 5. A process as in claim 1, wherein the macrolide compound is afforded by crystallization or precipitation.

